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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/772,661	02/05/2004	Yin-Xiong Li	275.00030103	5608

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EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/772,661	LI ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-21,23-51,73-76,78-92,96-109,113-120,123,127 and 128* is/are pending in the application.

4a) Of the above claim(s) *14,15,28-43,52-72 and 84-86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13,16-21,23-27,44-51,73-76,78-83,87-92,96-109,113-120,123,127 and 128* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Election/Restrictions

Claims 1-11, 13-21, 23-51, 73-76, 78-92, 96-109, 113-120, 123, 127 and 128 are pending. Claims 14, 15, 28-43, 52-72 and 84-86 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 6, 2005.

Claims 1-11, 13, 16-21, 23-27, 44-51, 73-76, 78-83, 87-92, 96-109, 113-120, 123, 127 and 128 are examined on the merits.

Response to arguments: Double Patenting

Claims 16, 17, 21, 27, 44-46, 51, 87-90, 92, 98-101, 108 and 109 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 6, 18, 39 and 48 of copending Application No. 10/038,984. This rejection is maintained for the reasons set forth in the office action mailed January 5, 2006. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The examiner acknowledges applicant's willingness to file a terminal disclaimer upon indication of allowable subject matter, but until such time maintaining the provisional rejection is proper.

New Claim Rejections - 35 USC § 112

Claim 78 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of this claim cannot be determined because it depends from claim 77, which is canceled.

Response to arguments: Claim Rejections - 35 USC § 112

Claims 1-11, 13, 18-21, 23-27, 51, 73-76, 78-83, 87-92, 96-109, 113-120 and 128 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of attenuating the expression of target genes in zebrafish cells in culture or zebrafish embryos, in avian neural crest tissue explant culture and in rat cell culture, does not reasonably provide enablement for attenuating gene expression *in vivo* in any non-embryonic animal. Moreover, the specification does not reasonably provide enablement for a method for treating a disease or infection in an organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection is maintained for the reasons set forth in the office action mailed January 5, 2006. Claims 73-75 are added to this rejection due to

applicant's amendment that overcomes the 112, second paragraph rejection of these claims.

Applicant traverses the scope of enablement rejection by arguing that the references relied upon by the examiner to describe the unpredictability of the RNA interference art at the time of filing are not supported by later findings, which support the opposite conclusion. Applicant describes the teachings of post-filing art that gene silencing with double stranded RNA is specific.

While the examiner agrees that much progress has been made in the field of RNA interference, these apparently contradictory teachings, as well as the references describing issues such as degree of attenuation, toxicity and possible immune responses, actually supports the argument that at the time of filing the field of RNA interference was in its infancy and that several questions regarding mechanism, specificity and side effects relating to predictability remained to be determined.

Applicant traverses the portion of the rejection referring to therapeutic methods by arguing that the claims are not directed to treating any specific disease and do not require that the resulting attenuation of gene expression has a therapeutic effect. The examiner acknowledges that the claims do not specifically recite therapy, but the instant methods do encompass therapeutic methods. The issues with regard to delivery of nucleic acids are not limited to those methods requiring therapeutic effects, but are generally applicable to any method performed in an organism.

With regard to delivery, applicant argues that the specification provides numerous details on delivery of dsRNA. Applicant further states that while cellular

uptake was a concern early in the development of nucleotide-based treatment, researchers have come to understand that cells readily internalize nucleic acids. These arguments are not persuasive because the guidance provided by the specification for delivery methods is generic and not recognized as specific to dsRNA. The examiner strongly disagrees with applicant's statements that cells readily internalize nucleic acids. The teachings of Agrawal that cellular uptake of an oligonucleotide is central to its efficacy is echoed by Opalinska et al., by Caplen and by Check, who describes that delivery methods are of concern to many researchers. In column 2 of page 11: " ...'The major hurdle right now is delivery, delivery, delivery' says Sharp" and in column 3 of the same page,

> "Khvorova believes that the medical benefits of RNAi will be huge if the delivery issues can be resolved. 'But we've looked at a lot of the delivery methods that have been used for antisense, and so far I haven't been impressed,' she says."

Applicant argues that the literature contains many examples of systemic delivery of antisense and cites the review of Wang et al. that describes how to target oligonucleotides for the liver. These arguments are not persuasive as targeting to a single organ is not predictive of targeting to all organs or cells.

Applicant asserts that the specification is enabling for the genus of target genes encompassed by the claims and cites the working examples of attenuation of expression of several genes in zebrafish embryos, one endogenous gene in avian neural crest tissue and one reporter gene in murine NIH/3T3 cells. These arguments are not persuasive because the disclosure provides examples of attenuation of gene expression of three vertebrate species while the claims are directed to all vertebrate

species, which number in the tens of thousands. Further, of the working examples in the specification, two of the three species were studied in cell culture while the claims encompass *in vivo* embodiments and it is these embodiments that are not enabled. Applicant also provides arguments regarding the suitability of the zebrafish as a model organism for human biology. While the zebrafish may be a model organism for studies of gene function, this does not speak to the ability of zebrafish to model human gene therapy.

Applicants state that a presumption exists that an application is enabled without evidence that undue experimentation is necessary to perform the claimed invention and further states they do not believe undue experimentation would be necessary to practice the invention. Applicant states that the steps of identifying gene sequences and producing RNA that will hybridize to the target are performed with methods routine to those in the art. This may be true, but the delivery of the RNA to cells of an organism is not routine. Applicant cites post-filing art as demonstrating dsRNA to be useful in "any non-embryonic vertebrate animal". While some examples exist in the art of use of double stranded RNAs, the state of the art is such that successful delivery of nucleic acid sequences to a target cell *in vivo* such that the oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically. The cited references do not provide evidence that delivery of a dsRNA to any organism is predictable or routine. The numerous references cited by the Examiner support that finding that methods of delivering nucleic acids to an organism in such a

way that the nucleic acids enters the targeted cell in a sufficient concentration and for a sufficient length of time to have a measurable effect are not routine and predictable.

Response to arguments: Claim Rejections - 35 USC § 102

Claims 1-5, 7, 9-11, 13, 16-21, 23-27, 44-51, 87-92, 96-101, 103, 104, 108, 109 and 113-116 are rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal et al. (of record). This rejection is maintained for the reasons set forth in the office action mailed January 5, 2006.

Applicant traverses the rejection over Agrawal et al. by asserting Agrawal does not teach administration of double stranded RNA to cells. To support this argument, applicant points to a passage on page 14 that states the oligonucleotides of Agrawal's invention activate RNase H and require four or more contiguous deoxyribonucleotides. This argument is not persuasive because the passage pointed out by applicant is describing that a preferred embodiment of Agrawal's invention contains deoxyribonucleotides in order to activate RNase H, the disclosure is not limited to this embodiment. As applicant states in their remarks, Agrawal et al. disclose on page 8 that the oligonucleotides can be ribonucleotides. Therefore, Agrawal et al. do disclose contacting cells with RNA.

Claims 1, 2, 6-11, 16-19, 21, 23, 24, 44, 45, 47, 48, 87-92 and 99-102 are rejected under 35 U.S.C. 102(b) as being anticipated by Cameron et al. (of record).

This rejection is maintained for the reasons set forth in the office action mailed January 5, 2006.

Applicant traverses the rejection over Cameron et al. by arguing that Cameron does not teach an RNA having a double stranded structure that includes a nucleotide sequence that hybridizes to a target gene. To support this argument, applicant points out that in the region of complementarity between a ribozyme and its target, the ribozyme itself is not double stranded, but single stranded. While the examiner agrees that this region of a ribozyme is not itself double stranded, the instant claims do not require that the portion of the RNA that hybridizes with the target gene be double stranded. The claims require only that the RNA comprises a double stranded structure and has a region that is complementary to the target. The ribozymes shown in figure 1 of Cameron et al. meet these limitations.

Claims 1-11, 13, 16-21, 23-27, 44-51, 73-76, 79-83, 87-92, 96-109, 113-120, 123 and 127 are rejected under 35 U.S.C. 102(e) as being anticipated by Fire et al. (of record). This rejection is maintained for the reasons set forth in the office action mailed January 5, 2006. Claims 73-76, 79-82, 120, 123 and 127 are added to the rejection due to the amendments made to these claims.

Claims 120, 123 and 127 are directed to methods of inhibiting gene expression in a cell by delivering a combination of two or more double stranded RNA molecules. Fire et al. disclose a method of inhibiting gene expression by administering double stranded RNA to a cell. Fire et al. disclose that the RNA can be up to 400 nucleotides in length.

As evidenced by the post-filing art of Zhang et al., Dicer is a multidomain ribonuclease that processes long dsRNAs to fragments of approximately 21 nucleotides during RNA interference. Although Fire et al. are silent as to the cleavage of long dsRNAs into double stranded duplexes approximately 21 nucleotides in length, the long dsRNA molecules disclosed by Fire et al. are necessarily cleaved into such duplexes, which would constitute a combination of two or more double stranded RNAs. As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. The claiming of an unknown property which is inherently present in the prior art does not necessarily make the claim patentable. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent in the prior art reference. This inherency argument is bolstered by *Schering Corp. v. Geneva Pharm. Inc.,* 339 F.3d 1373, 1377, 67USPQ2d 1664, 1668 (Fed. Cir. 2003). Inherent anticipation does not require recognition in the prior art. Since Fire et al. teach administering dsRNA and the resultant RNA interference, and it has since been discovered that this effect is mediated by the activity of Dicer, which cleaves long dsRNA into fragments that are approximately 21 nucleotides long, the teachings of Fire et al. anticipate the instant invention by disclosing a method that comprises delivering to a cell a combination of two or more double stranded RNAs.

In traversing the rejection over the Fire et al. reference, applicant argues that Fire's disclosure is not enabling for a method performed in vertebrate or mammalian

cells. Applicant points to the fact that Fire's working examples were performed in *C. elegans*, which is a primitive invertebrate. Applicant further argues that *C. elegans* is routinely grown on petri plates. While it is correct that the working examples described in Fire are directed solely to invertebrates, applicant has provided no evidence that the disclosure of Fire is not enabled for a method performed in mammalian cells. The existence of working examples is only one of the factors considered when assessing enablement of a disclosure; also considered are the guidance in the specification and the state of knowledge in the prior art. For example, Fire et al. disclose at column 5 that direct introduction into a cell is one method of administration and at column 8 that the dsRNA can be as short as 25 nucleotides in length. Like *C. elegans*, mammalian cells are routinely grown on petri plates and applicant has provided no evidence that direct administration of dsRNA to a mammalian cell as suggested by Fire et al. would not work.

Claims 1, 7-10, 16-18, 23, 73-76, 79-82, 87-89, 92 and 107 are rejected under 35 U.S.C. 102(e) as being anticipated by Graham (of record). Claims 73-75 and 79 are added to the rejection in view of the amendments to these claims.

Applicant traverses the rejection over Graham et al. by arguing the patent does not satisfy the 112, first paragraph enablement requirement. Applicant argues that Graham provides no working or prophetic examples of methods for delaying or repressing expression of a target gene in a mammalian cell but instead provides only methods for making plasmids. This argument is not persuasive because the existence

of working examples is only one of the factors considered when assessing enablement of a disclosure; also considered are the guidance in the specification and the state of knowledge in the prior art. While Graham's working examples may be directed to the creation of plasmids, Graham suggests at column 2 the use of these plasmids in an organism. Applicant further argues that it would have been unclear to the skilled artisan whether double stranded RNA would form in a cell after expression within the cell, citing possible binding by a protein that would prevent duplex formation and conditions in the cell that might prevent duplex formation. While cellular conditions could conceivably prevent formation of a duplex from two separate strands, Graham also discloses that the duplex can be formed by a hairpin. Applicant argues that it would also have been unclear to the skilled artisan if a hairpin double stranded RNA would be produced in a cell, but provides no evidence to support these assertions and no explanation of why the skilled artisan would doubt that a self-complementary oligonucleotide could form a duplex within a cell. Applicant further argues that the skilled person was aware of only a very little at the time Graham was filed, citing a review that speculates as to the extent of RNA interference in organisms other than *C. elegans*. While this review might teach that much about RNA interference was not known, it does not provide evidence that the methods of Graham do not work.

Applicant further traverses the rejection over Graham by asserting the reference does not teach every element of the claims. However, applicant has not specifically pointed out which elements of the claims are not taught, therefore the argument is not persuasive.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The central FAX Number is 571-273-8300.

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
September 29, 2006

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER